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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/225,718	01/06/99	TRECO D	07236/013004

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EXAMINER	
KETTER, J	
ART UNIT	**PAPER NUMBER**
1636	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/225,718	Applicant(s) TRECO ET AL.	
	Examiner James Ketter	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-168* is/are pending in the application.

4a) Of the above claim(s) *66-113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-168* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,9,12* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Claims 66-113 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15, filed 16 Janury 2001.

Applicant's election without traverse of Group II, claims 114-168 in Paper No. 15 is acknowledged.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 114-168 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the objection to the specification and associated rejection of the claims:

The nature of the invention. The claimed invention is drawn to a gene therapy method, particularly employing homologous recombination, i.e., "gene targeting", either in vivo or ex vivo.

The amount of direction or guidance presented in the specification, and the presence or absence of working examples. Applicants present general guidance in the form of short lists of

moieties which could exhibit targeting of the complexes to certain organs, or at least groups of cell types. Applicants give limited guidance for the selection of dosages, but these are not in view of any particular nucleic acid construct or genetic defect/disease. No teaching of actual amelioration of a disease state was set forth.

The state of the prior art. Orkin et al. (U) sets forth, as summarized at the first and second pages, item 3, that the Panel to Assess the NIH investment in Research on Gene Therapy (the "Panel") found that "clinical efficacy has not been definitively demonstrated at [that] time in any gene therapy protocol", that "[s]ignificant problems remain in all basic aspects of gene therapy", and that available vectors, and understanding in the art of the interactions between said vectors with the host, are inadequate.

Further, French Anderson (V) sets for the state of the art as of 30 April 1998, some considerable time after the filing date of the invention. Specifically, French Anderson makes clear that methods extant in the art, particularly vector selection, delivery methods and persistence of gene expression, were still inadequate to permit routine practice of gene therapy, let alone any demonstrably successful practice at all. Both the first paragraph, left-hand column, at page 25 and the conclusory paragraphs at page 30 make clear that French Anderson did not regard practice of gene therapy methods at all routine as of 30 April 1998.

Predictability or unpredictability of the art. Orkin et al. teaches that the Panel found that, at item 5, "[I]t is not always possible to extrapolate directly from animal experiments to human studies, Indeed, in some cases...animal models do not satisfactorily mimic the major manifestations of the corresponding human disease." Clearly, prediction of the success in the patient of a gene therapy protocol, where still only on paper, is not recognized in the art as

reliable. At the ninth page, under "Expression of transferred genes", it is taught that the expression level of genes after transfer into cells in vivo was problematic and poorly understood at the time of filing. Further, the editorial from Nature Biotechnology (hereinafter "the editorial", reference (W) on the attached PTO-892) and Verma et al. (X) demonstrate that gene therapy methods were not routine in the prior art. The editorial comments directly on the impact that Orkin et al. had on the field of gene therapy, showing that, while gene therapy is expected to be a useable field of therapy eventually, it clearly could not have been viewed as routine or even occasionally successful as of September 1997. Verma et al. establishes clearly, e.g., at page 242, final concluding paragraph, that gene therapy was not routine in the medical field as of September 1997.

Further, gene targeting suffered, at the time of the invention and at the present time as well, from a low rate of fidelity. Only a small fraction of transfection events actually target to the resident gene. Consequently, in an in vivo transfection method, an additional problem arises for the practice of the instant invention: that most of the cells in the tissue to be treated will not experience a targeted transfection event.

The quantity of experimentation. It is clear from Orkin et al., from the findings and recommendations of the Panel, and from the editorial and Verma et al., that a very large amount of experimentation of a complex nature will be required to develop any gene therapy protocol to the point of efficacy.

The breadth of the claim. The claimed methods, at the broadest, are drawn to treatment of any disease state with (presumably) any nucleic acid which would be useful in such treatment.

Given the relative infancy, if not non-existence, of (successful) gene therapy, such represents relatively very large breadth of the claims.

Were the skilled practitioner in the art to have attempted to practice the claimed methods, which are drawn to in vivo or ex vivo embodiments, i.e., gene therapy, said practitioner would have turned first to the specification for guidance in selecting dosages, treatment regimens and other factors which may bear upon the success of such treatment. However, as set forth supra, such guidance in the specification is limited in nature, and is insufficient with respect to prediction of proper levels of expression. Said practitioner then would have turned to the prior art, including that generally recited by the specification, to obtain detailed guidance for practice of the claimed methods. However, as set forth supra, the prior art does not recognize any clearly successful gene therapeutic methods. Thus, the skilled practitioner would not have been able to find the necessary guidance in the prior art. Finally, said practitioner would have been forced to turn to empirical experimentation to determine appropriate dosages, treatment regimens and other factors, required for successful practice of a gene therapy method. However, as set forth supra, the amount of experimentation recognized by the art as required for development of a successful gene therapy protocol is very large, with the assay for determining dosages set forth in the specification employing mere trial-and-error. Further, as set forth supra, the field of gene therapy is unpredictable. A large amount of experimentation in an unpredictable art with little or no available guidance is clearly undue experimentation.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official

Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993)(see 37 CFR § 1.6(d)). The Art Unit 1636 Fax number is (703) 305-7939. NOTE: If Applicant *does* submit a paper by fax to this number, the examiner must be notified promptly, to ensure matching of the faxed paper to the application file, and the original signed copy should be retained by Applicant or Applicant's representative. (703) 308-4242 or (703) 305-3014 may be used without notification of the examiner, with such faxed papers being handled in the manner of mailed responses. Applicants are encouraged to use the latter two fax numbers unless immediate action by the examiner is required, e.g., during discussions of claim language for allowable subject matter. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner with respect to the examination on the merits should be directed to James Ketter whose telephone number is (703) 308-1169. The examiner can normally be reached on M-F (9:00-6:30) Alternate Fridays Off.

Questions regarding formalities and processing of the case should be directed to Zeta Adams, whose telephone number is (703) 305-3291.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz, can be reached on 308-1133. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234.

jsk
January 28, 2001

JAMES KETTER
PRIMARY EXAMINER